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L2: Entry 28 of 50 File: USPT Apr 23, 2002

US-PAT-NO: 6375957
DOCUMENT-IDENTIFIER: US 6375957 B1

TITLE: Opioid agonist/opioid antagonist/acetaminophen combinations

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/400; 424/451, 424/464, 514/812

CLAIMS:

What is claimed is:

1. An oral dosage form, comprising

an orally therapeutically effective amount of

(A) an opioid agonist;

(B) acetaminophen; and

(C) an opioid antagonist;

the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount or in a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist.

2. The oral dosage form of claim 1, wherein the antagonist included in the oral dosage form causes an aversive experience in a physically dependent addict taking about 2-3 times said therapeutically effective amount.

3. The oral dosage form of claim 1, wherein the opioid agonist is hydrocodone and the antagonist is naltrexone.

4. The oral dosage form of claim 3, wherein the ratio of naltrexone to hydrocodone is from about 0.03:1 to about 0.27:1.

5. The oral dosage form of claim 3, wherein the ratio of naltrexone to hydrocodone is from about 0.05:1 to about 0.20:1.

6. The oral dosage form of claim 1, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, dihydrocodeine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

7. The oral dosage form of claim 1, further comprising an additional non-opioid drug selected from the group consisting of an NSAID, an NMDA receptor antagonist, a drug that blocks a major intracellular consequence of NMDA-receptor activation, dimenhydrinate or a pharmaceutically acceptable salt thereof, an antitussive, an expectorant, a decongestant, an antihistamine and mixtures thereof.

8. The oral dosage form of claim 1, further comprising one or more pharmaceutically acceptable inert excipients.

9. The oral dosage form of claim 6, wherein said opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, and mixtures thereof.

10. The oral dosage form of claim 6, wherein said opioid antagonist is naltrexone.

11. The oral dosage form of claim 1, further comprising a sustained release carrier that causes said opioid agonist to be released over a time period of about 8 to about 24 hours when orally administered to a human patient.

12. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is oxycodone, wherein the ratio of naltrexone to oxycodone is from about 0.037:1 to about 0.296:1.

13. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is codeine, wherein the ratio of naltrexone to codeine is from about 0.005:1 to about 0.044:1.

14. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is hydromorphone, wherein the ratio of naltrexone to hydromorphone is from about 0.148:1 to about 1.185:1.

15. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is levorphanol, wherein the ratio of naltrexone to levorphanol is from about 0.278:1 to about 2.222:1.

16. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is meperidine, wherein the ratio of naltrexone to meperidine is from about 0.0037:1 to about 0.0296:1.

17. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is methadone, wherein the ratio of naltrexone to methadone is from about 0.056: 1 to about 0.444:1.

18. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is morphine, wherein the ratio of naltrexone to morphine is from about 0.018:1 to about 0.148:1.

19. The oral dosage form of claim 11, wherein the sustained release carrier further causes said opioid antagonist to be released over a time period of about 8 to about 24 hours when orally administered to a human patient.

20. The oral dosage form of claim 19, wherein the sustained release carrier further causes the acetaminophen to be released over a time period of about 8 to about 24 hours when orally administered to a human patient.

21. The oral dosage form of claim 1, wherein the opioid agonist would be subtherapeutic if administered without the acetaminophen.

22. The oral dosage form of claim 1, wherein the acetaminophen would be subtherapeutic if administered without the opioid agonist.

23. The oral dosage form of claim 1, wherein the dosage form comprises from about 10 mg to about 2000 mg of acetaminophen.

24. The oral dosage form of claim 1, wherein the dosage form comprises from about 25 mg to about 1000 mg of acetaminophen.

25. The oral dosage form of claim 1, wherein the dosage form comprises from about 325 mg to about 1000 mg of acetaminophen.

26. The oral dosage form of claim 1, wherein the opioid agonist and the acetaminophen would each be subtherapeutic if not used in combination with each other.

27. The oral dosage form of claim 1, further comprising a sustained release carrier which causes the drugs to be released from the dosage form over a time period from about 8 hours to about 24 hours when the dosage form is orally administered to a human patient.

28. The oral dosage form of claim 27, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, dihydrocodeine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

29. The oral dosage form of claim 28, wherein said opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, and mixtures thereof.

30. The oral dosage form of claim 29, wherein the dosage form comprises from about 10 mg to about 2000 mg of acetaminophen.

31. The oral dosage form of claim 27, wherein either or both the opioid agonist and the acetaminophen would be subtherapeutic if not used in combination with each other.

32. A method of treating pain, comprising:

administering an oral dosage form which contains a therapeutically effective amount of

(A) an opioid agonist;

(B) acetaminophen; and

(C) an opioid antagonist;

the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but (i) is aversive in physically dependent human subjects when administered in the same amount or a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid analgesic together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist.

33. The method of claim 32, wherein the antagonist included in the oral dosage

form causes an aversive experience in physically dependent addicts taking about 2-3 times said therapeutically effective amount.

34. The method of claim 32, wherein the opioid agonist is selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, dihydrocodeine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof and the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmephene, cyclazocine, levallorphan, and mixtures thereof.

35. The method of claim 34, further comprising preparing said oral dosage form with a sustained release carrier such that the dosage form is administrable on a twice-a-day or on a once-a-day basis.

36. The method of claim 32, wherein the dosage form comprises from about 10 mg to about 2000 mg of acetaminophen.

37. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is oxycodone, wherein the ratio of naltrexone to oxycodone is from about 0.056:1 to about 0.222:1.

38. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is codeine, wherein the ratio of naltrexone to codeine is from about 0.0083:1 to about 0.033:1.

39. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is hydromorphone, wherein the ratio of naltrexone to hydromorphone is from about 0.222:1 to about 0.889:1.

40. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is levorphanol, wherein the ratio of naltrexone to levorphanol is from about 0.417:1 to about 1.667:1.

41. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is meperidine, wherein the ratio of naltrexone to meperidine is from about 0.0056:1 to about 0.022:1.

42. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is methadone, wherein the ratio of naltrexone to methadone is from about 0.083:1 to about 0.333:1.

43. The oral dosage form of claim 1, wherein said opioid antagonist is naltrexone and said opioid agonist is morphine, wherein the ratio of naltrexone to morphine is from about 0.028: 1 to about 0.111:1.

44. The oral dosage form of claim 1, further comprising an additional non-opioid drug selected from the group consisting of a COX-2 inhibitor and aspirin.

45. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is oxycodone, wherein the ratio of naltrexone to oxycodone is from about 0.056:1 to about 0.222:1.

46. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is codeine, wherein the ratio of naltrexone to codeine is from about 0.0083:1 to about 0.033:1.

47. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is hydromorphone, wherein the ratio of naltrexone to hydromorphone is from about 0.222:1 to about 0.889:1.

48. The method of claim 26, wherein said opioid antagonist is naltrexone and

said opioid agonist is levorphanol, wherein the ratio of naltrexone to levorphanol is from about 0.417:1 to about 1.667:1.

49. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is meperidine, wherein the ratio of naltrexone to meperidine is from about 0.0056:1 to about 0.022:1.

50. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is methadone, wherein the ratio of naltrexone to methadone is from about 0.083:1 to about 0.333:1.

51. The method of claim 26, wherein said opioid antagonist is naltrexone and said opioid agonist is morphine, wherein the ratio of naltrexone to morphine is from about 0.028:1 to about 0.111:1.

52. The oral dosage form of claim 1, wherein said combination decreases analgesia as assessed by direct measurement in patients or by use of one or more surrogate measures of opioid effect in human subjects.

53. The method of claim 26, wherein said ratio of opioid antagonist to opioid agonist decreases analgesia as assessed by direct measurement in patients or by use of one or more surrogate measures of opioid effect in human subjects.

54. A method of preventing oral abuse of an oral opioid formulation, comprising:

preparing an oral dosage form which comprises a therapeutically effective amount of

(A) an opioid agonist;

(B) acetaminophen; and

(C) an opioid antagonist;

the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but (i) is aversive in physically dependent human subjects when administered in the same amount or a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid analgesic together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist.

55. An oral dosage form, comprising:

an orally therapeutically effective amount of

(A) an opioid agonist;

(B) acetaminophen; and

(C) an opioid antagonist;

the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount or a higher amount than said therapeutically effective amount; and (ii) maintains or decreases analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic

together with the acetaminophen when administered to human patients without said opioid antagonist.

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L2: Entry 30 of 50 File: USPT Sep 25, 2001

DOCUMENT-IDENTIFIER: US 6294195 B1
TITLE: Orally administrable opioid formulations having extended duration of effect

Detailed Description Text (2):
The multiparticulate systems of the present invention may incorporate one or more compounds known as opioid analgesics. Opioid analgesic compounds which may be used in the present invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof, mixtures of any of the foregoing, mixed mu-agonists/antagonists, mu-antagonist combinations, and the like.

Detailed Description Text (4):
In one preferred embodiment the sustained-release opioid oral dosage form of the present invention includes hydromorphone as the therapeutically active ingredient in an amount from about 4 to about 64 mg hydromorphone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other hydromorphone salts or of the hydromorphone base. In other preferred embodiments where the opioid analgesic is other than hydromorphone, the dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect. For example, when the opioid analgesic comprises morphine, the sustained-release oral dosage forms of the present invention include form about 5 mg to about 800 mg morphine, by weight. When the opioid analgesic comprises oxycodone, the sustained-release oral dosage forms of the present invention include from about 5 mg to about 400 mg oxycodone.

Detailed Description Text (7):
The substrates of the present invention may further include one or more additional drugs which may or may not act synergistically with the opioid analgesics of the present invention. Examples of such additional drugs include non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Other suitable additional drugs which may be included in the dosage forms of the present invention include acetaminophen, aspirin, and other non-opioid analgesics.

Detailed Description Text (16):
In one preferred embodiment, the acrylic coating is an acrylic resin lacquers used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the Tradename Eudragit.RTM.. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit.RTM. RL 30 D and Eudragit.RTM. RS 30 D, respectively. Eudragit.RTM. RL 30 D and Eudragit.RTM. RS 30 D are copolymers

of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit.RTM. RL 30 D and 1:40 in Eudragit.RTM. RS 30 D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit.RTM. RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

Other Reference Publication (17):
Abraham Sunshine, et al., "Analgesic oral efficacy of tramadol hydrochloride in postoperative pain", Clin. Pharmacol. Ther., Jun. 1992, pp. 740-746.

CLAIMS:

5. The dosage form of claim 1, wherein said opioid analgesic is selected form the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, tramadol, and mixtures thereof.

6. The dosage form of claim 1, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.

16. A bioavailable sustained-release oral analgesic dosage form for once-a-day administration, comprising:

a unit dose comprising a plurality of pharmaceutically acceptable matrices comprising an analgesically effective amount of tramadol or a salt thereof, ethylcellulose and stearyl alcohol, each of said matrices having a diameter from about 0.1 mm to about 3 mm, said dosage form being bioavailable and providing a therapeutic effect for about 24 hours or more after oral administration to a human patient.

21. The dosage form of claim 1, wherein said opioid analgesic consists of tramadol or a salt thereof.

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L2: Entry 37 of 50 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245357 B1
TITLE: Extended release dosage form

Detailed Description Text (10):
In drawing FIG. 2, internal compartment 15 comprises a single homogenous composition. The compartment 15 comprises therapeutic agent 14, represented by dots. The term therapeutic agent as used herein included medicines or drugs, nutrients, vitamins, food supplements, and other beneficial agents that provide a therapeutic or a benefit to animals, including a warm-blooded animal, humans, farm animals, and zoo animals. Representative of drugs 14 comprises an opioid analgesic selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridne, benzylmorphine bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, diepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazone, ethoheptazine, ethylmethylthiambutene, ethylmorphine, propylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroenitabas, hydrocypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphone, phenazocine, phenoperidine, piminodine, pirtramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, and tilidine. The dose of opioid drug 14 is 0.1 .mu.g to 700 mg.

Detailed Description Text (11):
The opioid analgesic 14 can be present in compartment 15 alone, or the opioid analgesic 14 can be present with a nonopioid analgesic 14. Examples of nonopioid analgesic comprise a member selected from the group consisting of acetaminophen, aminobenzoate potassium, aminobenzoate sodium, aspirin, benoxaprofen, benzydamine, bicifadine decibuprofen, fenoprofen, flurbiprofen, ibufenac, indoprofen, ibuprofen, ketoprofen, naproxen, naproxol, salicylamide, sodium salicylate, and salicylate potassium. The dose of nonopioid analgesic 14 is 0.5 mg to 600 mg. An analgesic composition in compartment 15 comprises 1.0 mg to 750 mg of both the opioid analgesic and nonopioid analgesic.

Detailed Description Text (38):
where C.sub.x represents the molar concentration of any ion x in the solution and Z.sub.x represents the corresponding valence of ion x. Reference solutions of a simple salt such as sodium chloride can be prepared as the ionic strength reference. Since the value of each ionic charge Z is unity for sodium chloride, a value of one for the sodium ion and a value of one for the chloride ion, the ionic strength according to Equation 4 is directly proportional to molar concentration. A saturated solution of sodium chloride consists of 5.5 moles per liter and therefore has an ionic strength of 5.5 moles per liter. Such a saturated solution can be serially diluted with distilled water to produce a series of ionic strength reference solutions of any value less than 5.5 moles per liter for use in the reference cell to determine the effect of ionic strength on bilayer permeability as a function of ionic strength.

Detailed Description Text (57):
The hydromorphone-acetaminophen analgesic tablets are coated with an interior wall then coated by an exterior wall as follows: first, 154 g of ethyl cellulose having a molecular weight of 220,000 grams per mole and an ethoxyl content of 48.0 to 49.5 weight percent, and 112 g of hydroxypropylcellulose having a 80,000 molecular weight and a molar substitution of 3, and then 14 g of polyoxyethylene (40) stearate were dissolved with stirring in 3,720 g of anhydrous ethanol. The solution resulting was allowed to stand without stirring for 3 days, to provide the interior wall-forming

composition. Next, the exterior wall forming composition was prepared by dissolving 162.5 g of cellulose acetate having an acetyl content of 39.8 wt % and a molecular weight of 40,000 grams per mole, and 87.5 g of ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having a molecular weight of approximately 8,400 grams per mole and an ethylene oxide content of 82 wt % in 4,750 g of anhydrous acetone with stirring and slight warming to 26.degree. C. The resulting exterior forming wall composition was allowed to stand at ambient room temperature for one day.

Detailed Description Text (60):
Therapeutic compositions are manufactured by following the procedure of Example 2, to provide analgesic compositions comprising 1 mg to 1000 mg of an opioid selected from the group consisting of hydromorphone, hydromorphone base, hydromorphone salt, and hydromorphone derivatives; at least one nonopioid analgesic of 1 to 1000 mg selected from the group consisting of acetaminophen, aspirin, flurbiprofen, ibuprofen, indoprofen, benoxaprofen, propoxyphene, salicylamide, zenazocine and zomepirac; with the dose of opioid and nonopioid analgesic in the composition comprising 2 mg to 1000 mg; at least one polymeric carrier for both the opioid and nonopioid analgesics selected from 10 mg to 500 mg of a poly(alkylene oxide) comprising a 100,000 to 500,000 molecular weight represented by poly(methylene oxide), poly(ethylene oxide), poly(propylene oxide), poly(isopropylene oxide) and poly(butylene oxide); or a polymeric carrier of 10 mg to 500 mg of a carboxymethylene having a 7,500 to 325,000 molecular weight represented by a member selected from the group consisting of an alkali carboxymethylcellulose, and potassium carboxymethylcellulose, calcium carboxymethylcellulose, and potassium carboxymethylcellulose; 0.5 mg to 50 mg of a poly(vinyl) polymer possessing a 5,000 to 300,000 molecular weight as represented by poly(vinyl pyrrolidone),copolymer of poly(vinyl pyrrolidone and vinyl acetate), copolymer of poly(vinyl pyrrolidone and vinyl chloride), copolymer of vinyl pyrrolidone and vinyl fluoride), copolymer of poly(vinyl pyrrolidone and vinyl butyrate), copolymer of poly(vinyl pyrrolidone and vinyl laurate) and copolymer of poly(vinyl pyrrolidone and vinyl stearate); and 0 to 7.5 mg of a lubricant represented by a member selected from the group consisting of polyethylene glycol magnesium stearate, calcium stearate, potassium oleate, sodium stearate, stearic acid, and sodium palmitate. The therapeutic opioid-nonopioid dual analgesic composition may contain other composition forming ingredients, for example, colorants, compression aids such as microcrystallinecellulose, and binders such as starch. The analgesic composition can be compressed at a 1/8 to 3 ton-force to yield an orally administrable tablet.

Detailed Description Text (64):
A novel and useful therapeutic composition comprising 432 g of a morphine selected from the group consisting of morphine base, morphine pharmaceutically acceptable salt, pharmaceutically acceptable inorganic salt, pharmaceutically acceptable organic salt, morphine hydrobromide, morphine hydrochloride, morphine mucate, morphine N-oxide, morphine sulfate, morphine acetate, morphine phosphate dibasic, morphine phosphate monobasic, morphine inorganic salt, morphine organic salt, morphine acetate trihydrate, morphine bi(heptafluorobutyrate), morphine bi(methylcarbamate), morphine bi(pentafluoropropionate), morphine bi(pyridine-3-carboxylate), morphine bi(trifluoroacetate), morphine bitartrate, morphine chlorhydrate, and morphine sulfate pentahydrate, and 600 g of an analgesic selected from the group consisting of acetaminophen, aspirin, benoxaprofen, flurbiprofen, ibuprofen, indoprofen, propoxyphene, salicylamide, zenazocrine and zomepirac are blended with 963 g of poly(alkylene oxide) comprising a 300,000 molecular weight and 90 g of poly(vinyl pyrrolidone) having an average molecular weight of 40,000 are added to a mixing bowl and dry mixed for 12 minutes. Next, 404 g of denatured, anhydrous alcohol is slowly added to the blended composition forming materials with continuous mixing for 15 minutes. Then, the prepared granulation is passed through a 20 mesh screen, and allowed to dry at 25.degree. C. for 18 hrs, and then passed through a 16 mesh screen. The screened granulation is transferred to a planetary mixer, and with constant blending 14.9 g of calcium stearate is added to produce the therapeutic two analgesic composition. The composition is compressed into tablets comprising 350 mg of the therapeutic composition consisting of 70 mg of opioid analgesic and 100 mg of nonopioid analgesic and 180 mg of tablet forming materials. The tablets are compressed under 2.5 tons of pressure to provide a sustained release analgesic tablet.

Detailed Description Text (71):
Next, the bilayer cores, prepared immediately above, were then coated with the laminated membrane of this invention according to the following procedures: First, 154 grams of ethyl cellulose having a molecular weight of approximately 220,000 grams per mole and an ethoxyl content of 48.0 to 49.5 weight percent, 112 grams of hydroxypropyl cellulose having a molecular weight of 80,000 and a molar substitution of 3 and 14

grams of polyoxyethylene (40) stearate was dissolved in 3,720 grams of anhydrous ethanol formula with stirring. The resulting solution was allowed to stand without stirring for 3 days. This solution is referred to as the interior wall forming solution. A second solution was prepared by dissolving 162.5 grams of cellulose acetate having a acetyl content of 39.8 weight percent and an approximate molecular weight of 40,000 grams per mole and 87.5 grams of ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having molecular weight of approximately 8,600 grams per mole and an ethylene oxide content of 82 weight percent in 4,750 grams of anhydrous acetone with stirring and slight warming to 26 degrees centigrade. The resulting solution is the exterior-wall forming solution and it was allowed to stand at ambient room temperature for one day.

Detailed Description Text (87):
When placed in an aqueous environment, water is imbibed by osmosis into the dosage form dissolving the drug and salt to produce an internal osmotic pressure of 287 atmospheres and an ionic strength of 5.47 molar which osmotic pressure and ionic strength is maintained while the drug is dispensed until the last remaining portion of sodium chloride dissolves, at which point in time, the sodium chloride dilutes as a result of the water continuing to flow into the dosage form to lower levels of osmotic pressure and ionic strength, thereby allowing the pore former within the interior wall to dissolve and elute from the wall and thus increase permeability of the wall to compensate for the decrease in osmotic pressure as a result of the dilution. The dosage form meters the release of 8 milligrams of the analgesic at controlled rate over prolonged time.

CLAIMS:

5. A therapeutic solid, sustained-release composition comprising an opioid analgesic and a nonopioid analgesic, wherein the opioid analgesic comprises 0.1 .mu.g to 1000 mg of a member selected from the group consisting of hydromorphone and its pharmaceutically acceptable salts, the nonopioid analgesic comprises 1 mg to 1000 mg of a member selected from the group consisting of aspirin, flurbiprofen, ibuprofen, indoprofen, benoxaprofen, salicylamide, zenazocine and zomepirac, and 10 mg to 500 mg of a pharmaceutically acceptable poly(alkylene oxide) carrier.

10. A therapeutic solid, sustained-release composition comprising a first analgesic selected from the group consisting of morphine and its pharmaceutically acceptable salts, a second analgesic selected from the group consisting of acetaminophen, aspirin, benoxaprofen, flurbiprofen, ibuprofen, indoprofen, salicylamide, zenazocine, and zomepirar, and a pharmaceutically acceptable poly(alkylene oxide) carrier.

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L2: Entry 42 of 50 File: USPT Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968551 A
TITLE: Orally administrable opioid formulations having extended duration of effect

Detailed Description Text (2):
The multiparticulate systems of the present invention may incorporate one or more compounds known as opioid analgesics. Opioid analgesic compounds which may be used in the present invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof, mixtures of any of the foregoing, mixed mu-agonists/antagonists, mu-antagonist combinations, and the like.

Detailed Description Text (4):
In one preferred embodiment the sustained-release opioid oral dosage form of the present invention includes hydromorphone as the therapeutically active ingredient in an amount from about 4 to about 64 mg hydromorphone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other hydromorphone salts or of the hydromorphone base. In other preferred embodiments where the opioid analgesic is other than hydromorphone, the dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect. For example, when the opioid analgesic comprises morphine, the sustained-release oral dosage forms of the present invention include from about 5 mg to about 800 mg morphine, by weight. When the opioid analgesic comprises oxycodone, the sustained-release oral dosage forms of the present invention include from about 5 mg to about 400 mg oxycodone.

Detailed Description Text (7):
The substrates of the present invention may further include one or more additional drugs which may or may not act synergistically with the opioid analgesics of the present invention. Examples of such additional drugs include non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Other suitable additional drugs which may be included in the dosage forms of the present invention include acetaminophen, aspirin, and other non-opioid analgesics.

Detailed Description Text (16):
In one preferred embodiment, the acrylic coating is an acrylic resin lacquers used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the Tradename Eudragit.RTM.. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit.RTM. RL 30 D and Eudragit.RTM. RS 30 D, respectively. Eudragit.RTM. RL 30 D and Eudragit.RTM. RS 30 D are copolymers

of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit.RTM. RL 30 D and 1:40 in Eudragit.RTM. RS 30 D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit.RTM. RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

Other Reference Publication (25):
Abraham Sunshine, et al., "Analgesic oral efficacy of tramadol hydrochloride in postoperative pain", Clin. Pharmacol. Ther., Jun. 1992, pp. 740-746.

CLAIMS:

6. The dosage form of claim 1, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.

39. The dosage form of claim 18, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

40. The dosage form of claim 30, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

41. The method of claim 13, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

42. The method of claim 33, further comprising incorporating a therapeutically effective amount of aspirin or acetaminophen into said unit dose.

45. The method of claim 3, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.

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6,407,135

L2: Entry 26 of 50 File: USPT Sep 17, 2002

DOCUMENT-IDENTIFIER: US 6451806 B2
TITLE: Methods and compositions involving opioids and antagonists thereof

Detailed Description Text (28):
In accordance with the present invention, there are provided methods which comprise administering to a patient, inter alia, an opioid compound. A wide variety of opioids are available which may be suitable for use in the present methods and compositions. Generally speaking, it is only necessary that the opioid provide the desired effect (for example, pain alleviation), and be capable of being incorporated into the present combination products and methods (discussed in detail below). In preferred embodiments, the present methods and compositions may involve an opioid which is selected from alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and/or tramadol. More preferably, the opioid is selected from morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and/or tramadol.

Detailed Description Text (29):
The opioid component of the present compositions may further include one or more other active ingredients that may be conventionally employed in analgesic and/or cough-cold-antitussive combination products. Such conventional ingredients include, for example, aspirin, acetaminophen, phenylpropanolamine, phenylephrine, chlorpheniramine, caffeine, and/or guaifenesin. Typical or conventional ingredients that may be included in the opioid component are described, for example, in the Physicians' Desk Reference, 1999, the disclosures of which are hereby incorporated herein by reference, in their entirety.

Detailed Description Text (174):
A double-blind Phase II clinical study in 24 young healthy patients undergoing third molar extraction dental surgery showed that the compound of formula (II) (4 mg total oral dose) did not antagonize analgesia or pupil constriction produced by intravenous morphine sulfate. No patients were withdrawn for adverse effects.

CLAIMS:

18. A method according to claim 1 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

19. A method according to claim 18 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

40. A method according to claim 25 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

41. A method according to claim 40 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

64. A method according to claim 47 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

65. A method according to claim 64 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

99. A composition according to claim 83 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

100. A composition according to claim 99 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

117. A composition according to claim 102 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

118. A composition according to claim 117 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

136. A kit according to claim 120 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

137. A kit according to claim 136 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

154. A kit according to claim 139 wherein said opioid is selected from the group consisting of alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, sufentanil and tramadol.

155. A kit according to claim 154 wherein said opioid is selected from the group consisting of morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl and tramadol.

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L2: Entry 26 of 50 File: USPT Sep 17, 2002

US-PAT-NO: 6451806
DOCUMENT-IDENTIFIER: US 6451806 B2

TITLE: Methods and compositions involving opioids and antagonists thereof

DATE-ISSUED: September 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Farrar; John J.	Chester Springs	PA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Adolor Corporation	Exton	PA			02

APPL-NO: 09/ 725661 [PALM]
DATE FILED: November 29, 2000

PARENT-CASE:
This application was filed as a continuation-in-part of U.S. application Ser. No. 09/450,806, filed Nov. 29, 1999, which was converted to U.S. provisional application Ser. No. 60/304,199.

INT-CL: [07] A61 K 31/44

US-CL-ISSUED: 514/282; 514/295, 514/315, 514/318, 514/316, 514/320, 514/331
US-CL-CURRENT: 514/282; 514/295, 514/315, 514/316, 514/318, 514/320, 514/331

FIELD-OF-SEARCH: 514/315, 514/282, 514/316, 514/318, 514/320, 514/331, 514/295

PRIOR-ART-DISCLOSED:

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Search Selected | Search ALL

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ART-UNIT: 1614

PRIMARY-EXAMINER: Reamer; James H.

ABSTRACT:

Novel methods and compositions comprising opioids and opioid antagonists. In preferred embodiments, the methods and compositions comprise opioids and peripheral mu opioid antagonist compounds. The methods and compositions are particularly suitable for treating and/or preventing side effects associated with opioids including, for example, constipation, vomiting and/or nausea.

164 Claims, 3 Drawing figures